Letter to the Editor: Haematologic Toxicity During Craniospinal Irradiation—The Impact of Prior Chemotherapy

I read with interest the manuscript by Marks et al. [1]. The authors were kind enough to refer to my own work [2]. Comparison and summation of these two sets of observations are of interest, particularly in an era when growth factors may ameliorate the manifestations of myelosupression as it appears in the peripheral blood count—importantly, not necessarily the same parameter as integral bone marrow reserve.

In my observations of 23 medulloblastoma patients (mean age, 9 years; median age, 6 years) who received a mean dose of 31 Gy in 24 fractions (of 1.25 Gy per fraction) in 41 days, I was fortunate to have serial differential leukocyte count assessments and summarize the findings as follows. No patients in this group had received prior chemotherapy. The peripheral leukocyte count before therapy ($8.6 \pm 0.8\,10^9$/l) was halved by 7.5 Gy (cord) because of the rapid disappearance of lymphocytes (which halved their circulating numbers by 5 Gy) and neutrophils (which halved their circulating numbers by 7.5 Gy). Monocytes exhibited an early dip in their circulating numbers, but thereafter tended to recover and proved overall the most refractory lineage. Following its early decline, the neutrophil count was maintained at the 3×10^9/l level, and a plateau was observed. The platelet count (pretherapy, $349 \pm 28 \times 10^9$/l) fell gradually from the start of radiotherapy, but levels below 200×10^9/l were not encountered before the patient had already experienced leukopenia; no patient experienced absolute thrombocytopenia. The hemoglobin declined gradually during neuraxis radiotherapy and was significantly lower at 35 Gy (10.2 ± 0.4 g/dl) than before therapy (12.0 ± 0.3 g/dl $\times 10^9$/l). Absolute eosinophilia (up to 3.38×10^9/l) was observed during (two patients) or within 1 week after (one patient) neuraxis radiotherapy—a phenomenon first described by Levitt in 1932 at St. Bartholomew's Hospital [3].

After completion of radiotherapy, there was no evidence of myeloid recovery at 1 week, but the peripheral count had normalized by 1 or 2 months.

The effects of prior chemotherapy were probed in my analysis of a population of conventionally fractionated, extended portal radiotherapy patients, viz., total nodal irradiation and mantle or inverted-Y patients with Hodgkin's diseases. No patient had marrow infiltration. The leukocytosis and thrombocytosis consequent to splenectomy were less in the patients who had received prior chemotherapy. During radiotherapy, the leukocyte count and platelet nadirs were lower in the prior chemotherapy patients, and TNI within 2 years of chemotherapy proved sufficiently toxic to curtail the radiotherapy treatment, this time often due to thrombocytopenia. Following extended portal radiotherapy in prior chemotherapy patients, the peripheral blood count recovery was slow (months). This study population had a mean age of 25 years (mean, 24 years; range 7–45 years), so the red marrow was proportionately more heavily concentrated in the axial skeleton.

The observations of Marks et al. [1] build on these observations, with regard to a prior chemotherapy group of 17 neuraxis radiotherapy children (mean age, 6.9 years; median age, 3.6 years; age range 1.5–23 years). These patients were compared with a similar group of 20 neuraxis radiotherapy children (mean age, 9.7 years; median, 9 years; range, 0.8–23 years). In patients without prior chemotherapy, the nadir counts (total leukocyte count, 2.7×10^9/l; platelet count, 148×10^9/l) were comparable to my own observations. The patients receiving prior chemotherapy started radiotherapy with statistically similar total leukocyte counts and platelet counts. The ratio between the nadir counts and pretreatment values was lower in the prior chemotherapy group, although the difference did not reach levels of statistical significance. The rate of decline in the peripheral blood count was significantly faster with increasing neuraxis radiation dose in the prior chemotherapy patients than in the "no chemotherapy" group. The effects were more noticeable in patients who had received four or more courses of chemotherapy. The reason for these authors' observations on the effect of prior chemotherapy being less dramatic than my own in Hodgkin's patients can probably be explained by the higher cumulative dose of prior chemotherapy ($6 \times$ MVPP) and the older patient population (i.e., red marrow being more heavily concentrated in the axial skeleton) in my study population.

The synthesis of both sets of data demonstrates a long-term damaging effect of chemotherapy and extended portal radiotherapy on the bone marrow reserve. The same would be expected following total body irradiation on total bone marrow reserve. I am by no means certain that the administration of growth factors will do more than assist in a "little temporary blood count difficulty" (e.g., holding the neutrophil or platelet count above some critical basal value). It would not be expected that they would improve the underlying bone marrow "fragility" or its reserve. They might even make the marrow situation worse (vide infra).

For clinicians interested in growth factor administra-

tion as an integral part of increasing the therapeutic changes of sequenced chemoradiotherapy programs, there is much to learn from early rodent radiobiology—whole body with single tibial shielding radiation studies [4–6]. It was shown that an early drop in marrow CFU (uncommitted stem cells) in the shielded marrow was due to an increased population of CFU_c (committed descendants). The underlying marrow reserve (CFU) was diminished. In subsequent work from Barts there was more direct evidence for late CFU damage [7]. Mice received no irradiation, 8 Gy whole body, or 8 Gy plus 5×10^5 syngeneic bone marrow cells. Eight months later, there appeared to be no differences in the marrow CFU in all three groups, but there was more active cell cycle activity in the irradiation only group. Furthermore, when marrow was used to rescue lethally irradiated syngeneic recipient mice, the previously irradiated bone marrow was less able to rescue the recipient mice than the control marrow.

There is no doubt that wide field radiation to the red marrow (either as part of total body irradiation or as part of orthodox treatment for other diseases such as medulloblastoma) has lasting effects on marrow reserve. The clinical data reviewed here demonstrate that chemotherapy has a similar effect (as unmasked by later wide field radiation). Whereas radiotherapy effects are on specific sites of red marrow, with chemotherapy the effect is diffuse. Whether the current interest in growth factors will alter this underlying situation is unclear. It is certain that such treatment can help the clinician out of a little temporary blood count difficulty and allow completion of radiotherapy within a specified prescription time. However, the previously discussed rodent radiobiology experiments might suggest that the bone marrow reserve may be diminished by growth factor stimulated CFU to CFU_c progression. The most important aspect of the clinical observations by Dr. Marks and myself may be with regard to increasing our knowledge of marrow reserve. Future research is clearly needed.

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Letter to the Editor: Nephron Sparing Surgery for Unilateral Wilms' Tumor

The recent report from the National Wilms' Tumor Study Group [1] does not recommend a prospective trial to determine the impact of nephron sparing surgery on treatment outcome of children with unilateral nephroblastoma and a normal contralateral kidney. This conclusion is supported by the low incidence of renal failure found in a large number of children and adolescents following treatment for unilateral Wilms' tumor. The main concern is that renal failure may develop during adult life.

Nephron sparing procedures remain, therefore, an option for only a limited number of children with unilateral nephroblastoma. Reasonable criteria for nephron sparing surgery in unilateral nephroblastoma may be drawn from previous experience in the treatment of renal cell carcinoma. In adults with unilateral low stage and small renal cell carcinoma, the mortality and recurrence rate following partial nephrectomy or even simple enucleation are comparable to those following radical nephrectomy [2–4]. This approach seems even more reasonable in children with nephroblastoma, since chemotherapy is known to minimize the risk of relapse in nephrectomized children with residual microscopic disease.

We, therefore, investigated the feasibility of tumor enucleation in children with Stage I nephroblastoma and a normal contralateral kidney. Possible candidates for enucleation surgery were evaluated according to the following criteria: 1) Stage I at diagnosis; 2) well-defined margins on post-contrast CT scan; and 3) at least 50% of functioning preservable kidney. Chemotherapy was given pre- and post-operative in all patients. In our experience, enucleation is a safe and simple surgical technique which is effective for both polar or centrally located

tumor. Preliminary results suggest that this approach seems a reasonable option for Stage I unilateral Wilms' tumor [5,6].

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Letter to the Editor: Response to Letter by Cozzi and Schiavetti

We (the authors) recognize that a number of centers are employing protocols for the use of nephron sparing surgery in children with unilateral nephroblastoma. The purpose of our review was to establish the known risk of renal failure following treatment of Wilms' tumor. The National Wilms' Tumor Study Group has a long-standing commitment to track the late effects of children treated for this disease. The incidence of renal failure that we reported is the best data that is known, to date, in such a large series of patients. It will be many years before all of these patients reach late adulthood and we will be able to determine the exact risk of late clinical renal insufficiency. However, with follow-up ranging up to 25 years, we have noted a very low risk for patients with unilateral tumors.

The letter by Cozzi and Schiavetti referred to the experience with renal cell carcinoma. There is a difference between the latter patients and those with Wilms' tumor. Patients with renal cell carcinoma that are amenable to partial nephrectomy have small tumors at diagnosis. Most Wilms' tumor patients require preoperative chemotherapy to facilitate partial resection. The experience in bilateral tumors suggests that this can be feasible [1]. The National Wilms' Tumor Study Group believes that this is an acceptable treatment for bilateral tumors, given the known increased incidence of renal failure in this group of patients. However, in order to employ this approach for unilateral tumors, one would then have to weigh the small known risk of renal failure in this group vs. the problems with inaccurate staging following chemotherapy [2,3]. Therefore, we have not considered it necessary to adopt such an approach to date.

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Letter to the Editor: Tropisetron in the Prevention of Nausea and Vomiting in 131 Children Receiving Cytotoxic Chemotherapy

I have read with interest the report by Benoit et al. [1] concerning the efficacy of tropisetron in the prevention of nausea and vomiting in children receiving cytotoxic chemotherapy, which appeared in the last issue of the journal.

In a recent study [2], I have also evaluated the antiemetic efficacy of tropisetron in 15 children with malignant disease who have received cisplatin (CDDP) either alone (1/15) or in combination (14/15) with other highly emetogenic cytotoxic drugs (Table 1). The dose of CDDP ranged between 80–120 mg/m2/day. The administration of tropisetron, dosage and the grading scale used were same as the authors' study. Patients were followed for 5 days. Complete control on day 1 was obtained in 53.3% of patients and partial control in 40%. Complete control on days 2 to 5 was observed in 40 to 80% of patients and partial control was observed in 20 to 46.6%. There were no side effects.

The authors suggested that their study was the first report on the use of tropisetron in infants. To my knowledge, Cefalo et al. [3] also studied two infants with neuroblastoma who were treated with etoposide, vincristine, and epirubicin. They have found tropisetron to be a valid, safe, and manageable antiemetic. Also in my study, there were two infants. I agree with the authors that the efficacy and safety data was similar to those reported for older children.

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